Claim 1 has been amended and claims 98-100 deleted to remove all references to "non-hygroscopic dry powders." Instead, the composition of claim 1 now optionally includes one or more "non-hygroscopic additives," a feature fully supported at page 14, lines 25-32 of the specification.

The composition of claim 1 has been narrowed by the use of the transitional term "consisting essentially of" instead of "comprising." Consequently, the composition of claim 1 now includes "one or more surfactant compounds," which is supported at page 10, lines 7-10 and page 4, line 29 of the specification.

The optional "agglomerates" limitation in claim 1 has been deleted and re-introduced as new dependent claim 101.

Claims 1, 2, 12, 13, 16, 31, 56, and 76 have been amended to modify dependencies, change terms to establish antecedent basis, or otherwise remedy inadvertent errors.

No new matter has been added by the above amendments.

Obviousness-Type Double Patenting Rejection

Claims 1-3, 11-16, and 61-100 have been rejected for obviousness-type double patenting over claims 1-33 of U.S. Patent No. 5,581,998. In addition, claims 21, 22, 28-32, and 51-100 are rejected for obviousness-type double patenting over claims 1-20 of U.S. Patent No. 5,506,203. Claims 11 and 98-100 have been cancelled. To overcome both of these rejections, the common assignee of record for this application and the two cited U.S. patents has executed the enclosed Terminal Disclaimer under 37 C.F.R. §§ 3.73(b) and 1.321(b). The Terminal Disclaimer is being submitted with the proper fee.

Rejections under 35 U.S.C. § 112, First Paragraph

I

Claims 1-16, 21, 22, 26-32, and 50-100 have been rejected for lacking enablement for "pharmaceutical" uses of the claimed invention. Claims 11 and 98-100 have been cancelled. With respect to the remaining claims, applicants traverse the enablement rejection on the ground that the claims, as amended above, no longer are limited to "pharmaceutical" uses.

According to the Examiner,

> The term 'pharmaceutical' indicates pharmaceutical use of the composition in treatment of disease. The specification clearly does not teach how to use the pharmaceutical composition in the treatment of any disease (page 4 of the Office Action).

To overcome this rejection, applicants have removed all reference to "pharmaceutical" uses in the pending claims. Applicants note that non-pharmaceutical uses of the invention, i.e., *in vitro* and *in vivo* biological screening of the compositions for absorption efficiency, are described at Examples 1 and 2, pages 19-21 of the specification.

Thus, the compositions, methods, and devices of the invention can be used to test any combination of polypeptide and enhancer for efficacy in, e.g., a test animal model. As such testing methods are fully enabled at pages 19-21 of the specification, the pending claims, as amended, are also enabled. Accordingly, applicants respectfully request withdrawal of this rejection.

II

Claims 1-16 and 98-100 are rejected as relying on the term "non-hygroscopic dry powder" which, according to the Examiner, is new subject matter not described in the specification. Claims 11 and 98-100 have been cancelled. The term "non-hygroscopic dry powder" has been deleted in favor of a reference to "one or more non-hygroscopic additives" by the above amendment, thereby rendering the rejection moot. As discussed above, the new term is fully supported in the specification.

Since claims 2-10 and 12-16 were rejected because they depend on claim 1, the rejection of claims 2-10 and 12-16 on this ground is also moot.

Rejection under 35 U.S.C. § 102(b)

Claims 1 and 3-12 are rejected as anticipated by Schipper et al. (Pharm. Res. 10:682-686, 1993). Claim 11 has been cancelled. Applicants traverse the rejection with respect to the remaining claims, on the ground that Schipper's large particles are not the same, and are not encompassed by, either applicants' smaller particles (as in amended claim 1) or applicants' agglomerates (as in new claim 101).

The Examiner maintains that Schipper's composition anticipated claim 1 as originally presented because Schipper teaches agglomerates of the smaller particles required in claim 1. In support of her rejection, the Examiner states:

> The composition is "comprising" and is optionally agglomerates. The dry powder composition is "comprising" and is not limited to processed primary particles where 50% of the total mass of active compounds are

primary particles of 10 microns or less. Applicants' declaration is not persuasive because it does not provide evidence to support the opinion that the agglomerates of the art are different from the claimed compositions. (Section 8, page 6 of the Office Action)

To clarify the issues, applicants have amended claim 1 by deleting reference to optional agglomerates. Claim 1 requires primary particles having a diameter less than or equal to about 10 microns. As discussed below, Schipper does not describe such primary particles, and so does not anticipate claim 1 or any claim which depends therefrom.

By way of background, it is noted that "primary particle" and "agglomerate" are distinct terms to one skilled in the art of pharmacology. Very small (under 10 μm) primary particles, such as those specified in the claims, are necessary for efficient delivery deep into the lower respiratory tract, but are also often flyaway and difficult to handle due to their low mass. To overcome this problem, primary particles are sometimes formed into relatively large, loose agglomerates for handling and storage purposes, and then de-agglomerated into the individual primary particles at the point of inhalation. These loose agglomerates are akin to the clumps that appear in wheat flour, a common household powder. Like loose clumps of wheat flour, the agglomerates of applicants' primary particles crumble into individual primary particles when subjected to light turbulence (e.g., in a device such as a Turbuhaler™ inhaler). In contrast, breaking up a primary particle into smaller pieces would require application of a great deal more force. An analogy that comes to

mind is a comparison between a fist-sized clump of damp sand (i.e., an agglomeration of very small "primary particles"), vs. a fist-sized rock (a single, large "primary particle").

With this background in mind, it is noted that Schipper's powder is produced by providing an insulin/enhancer solution, which was "then frozen in liquid N_2 and lyophilized" (col. 2, page 682, under "Preparation of Nasal Dosage Forms"). As described in paragraph 7 of the Declaration of Kjell Bäckström submitted with the response filed October 28, 1998, this relatively simple method of powder preparation would produce particles much larger than those recited in claim 1. The method would not produce primary particles of less than 10 microns in any significant amount, as required in claim 1. To produce smaller primary particles, Schipper's lyophilized powder would have had to have been subjected to an additional processing step such as jet milling. Schipper does not describe any additional processing steps that could result in primary particles having the size specified in claim 1.

Nor would he have had any reason to carry out such processing. Since Schipper is interested in administering his powder solely via an intranasal route (see, e.g., col. 1, page 683, last complete sentence; and page 682, abstract), the relatively large particles produced by lyophilization would be suitable as is for his desired mode of administration. Thus, Schipper would have no motivation to further process his powder to arrive at applicants' smaller primary particles, which are meant for deposition in the lower respiratory tract. In fact,

Schipper would shun any further processing that would produce smaller particles because such particles would travel further down the respiratory tract instead of being lodged in the nasal cavities, and also would be more difficult to handle.

As discussed above, Schipper's powder contains primary particles which are substantially larger than the primary particles recited in claim 1. Thus, Schipper does not anticipate claim 1. As claim 1 is not anticipated, neither are claims 3-10 and 12, all of which depend from claim 1.

Claim 101 has been added to specify that the primary particles in claim 1 are agglomerated, i.e., temporarily associated in friable clumps. In regards to claim 101, applicants note that it is not reasonable to suggest that Schipper's particles are merely agglomerates of primary particles less than or equal to 10 micron in diameter. As discussed above, large primary particles (such as those apparently produced by Schipper) are fundamentally different from loosely associated agglomerates of smaller primary particles. Thus, Schipper does not anticipate claim 101.

CONCLUSION

Applicants submit that all of the claims are now in condition for allowance, which action is requested. Filed herewith is a Petition for Automatic Extension with the required fee and a check for $130 for submission of the Terminal Disclaimer.

Please charge any additional fees, or make any credits, to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 6-22-99

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